A Computer Simulation of the Hypothalamic-Pituitary-Adrenal Axis

Joseph Gonzalez-Heydrich M.D.[1], Ronald J. Steingard M.D.[1], Isaac Kohane M.D., Ph.D.[2]
Psychopharmacology Clinic, Departments of Psychiatry [1] and Division of Endocrinology, Department of Medicine [2], Children's Hospital, Boston

This paper describes the construction of a computer model that simulates the hypothalamic-pituitary-adrenal axis (HPA axis) regulation of cortisol production. It is presented to illustrate the process of physiological modeling using standard "off the shelf" technologies. The model simulates components of the HPA axis involved in the continuous secretion and elimination of cortisol, adrenocorticotropin (ACTH), and corticotropin releasing hormone (CRH). The physiological relations of these component pieces were modeled based on the current knowledge of their functioning. Rate constants, half lives, and receptor affinities were assigned values derived from the experimental literature. At its current level of development the model is able to accurately simulate the timing, magnitude and decay of the ACTH and cortisol concentration peaks resulting from the ovine-CRH stimulation test in normal and hypercortisolemic patients. The model will be used to predict the effects of lesions in different components of the HPA axis on the time course of cortisol and ACTH levels. We plan to use the model to explore the experimental conditions required to distinguish mechanisms underlying various disorders of the HPA axis, particularly depression. Efforts are currently underway to validate the model for a large variety of normal and pathological perturbations of the HPA axis.

INTRODUCTION:

The HPA regulation of cortisol is accomplished through a complex network of interacting components. Despite increasingly detailed knowledge about each of these components, it remains difficult to predict from this information how the network will perform. One possible approach to understanding network functioning is to build a simulation that allows us to model, quantitatively, the functioning of these components within the context of the network [1].

METHODS / RESULTS

Extend, (Imagine That, Inc. San Jose, Ca.) a simulation development tool was used to build the simulations on a macintosh computer. The granularity of mechanistic detail modeled was chosen to simulate the time course of ACTH and cortisol plasma levels observed during a standard test of HPA functioning, the Ovine-CRH stimulation test (oCRH stim. test). The following are the differential equations used:

Cortisol module: Eq. (1)

$$d[\text{cortisol}]/dt = k_1*[\text{ACTH}] + k_2 - k_3*[\text{cortisol}]$$

ACTH module: Eq. (2)

$$d[\text{ACTH}]/dt = k_4*[\text{CRH}]+k_5 - k_6*[\text{ACTH}]-(k_4*[\text{CRH}]+k_5)*I_{max}*[\text{cortisol}]/(K_d+[\text{cortisol}])$$

CRH module: Eq. (3)

$$d[\text{CRH}]/dt = \text{pulse function},f(t) + k_7 - k_8[\text{CRH}]$$

Where [X] is concentration of X. k_n is a rate constant. I_{max} is the saturation level of inhibition. K_d is the dissociation constant for the glococorticoid II receptor (only inhibition at the level of the pituitary by cortisol was modeled [2]). The constants were estimated from published oCRH stim. tests in normal controls.

The results of the simulations were compared to published results of the oCRH stim. test in normal controls and patients with acute and chronic hypercortisolemia[3]. The program was able to successfully simulate 1) the plasma half lives of cortisol and ACTH and 2) the magnitude and timing of their peaks in response to an oCRH stimulation test in normal individuals and patients with hypercortisolemia .

This paper discusses the implementation with "off the shelf" software, of simulations that closely follow clinical and experimental observations. To proceed in further building this tool, we plan to generate a range of models and selecting the *minimal* or *optimal* model by applying formal criteria [1]. Fitting the constants of this model to actual patient's diagnostic tests should allow the estimation of otherwise inaccessible physiologic parameters and serve as guides to further basic and clinical research.

REFERENCES

[1] Carson, C. Cobelli and L. Finklestein. The Mathematical Modeling of Metabolic and Endocrine Systems. John Wiley and Sons. New York. 1983.
[2] Dayanithi and F. A. Antoni. Rapid as well as Delayed Inhibitory Effects of Glucocorticoid Hormones on Pituitary Adrenocorticotropic Hormone Release are Mediated by Type II Glucocorticoid Receptors and Require Newly Synthesized Messenger Ribonucleic Acid as well as Protein. Endocrinology 1989;125:308-13.
[3] B. Martin and S. Reichlin. Clinical Neuroendocrinology. F. A. Davis. Philadelphia. 1987.

0195-4210/94/$5.00